

02.01.69 Treatment of Congenital Athymia (Rethymic®)

Original Effective Date: December 2022

Review Date: December 2025

Revised: December 2024

DISCLAIMER/INSTRUCTIONS FOR USE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

Related Policies:

- None

Summary

Description

Congenital athymia is an ultra-rare condition in which infants are born without a functioning thymus. The thymus is crucial for the development, selection, and maturation of T cells, which are essential in effectively fighting infection and regulating the immune system. Without a functioning thymus, children develop severe immunodeficiency, susceptible to life-threatening infections. Without adequate medical treatment and management, children with congenital athymia usually do not live past the first few years of life. Multiple genetic and syndrome disorders, mutations and deficiencies are associated with congenital athymia. Supportive care, such as strict prevention measures, prophylactic antimicrobials, immunoglobulin replacement and isolation have been the mainstay management of children with congenital athymia. Allogeneic processed thymus tissue-agdc (Rethymic) is a regenerative tissue-based

therapy that is indicated for immune reconstitution in pediatric patients with congenital athymia. The reengineered tissue is implanted in the thigh muscle to help a child with congenital athymia build a functioning immune system to reduce the number of potentially life-threatening infections.

Summary of Evidence

For individuals with congenital athymia who received allogeneic processed thymus tissue-agdc, the evidence included 10 prospective, single-center, open-label studies evaluating a total of 95 participants. Relevant outcomes are disease-specific survival, change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The primary evidence of efficacy was based on a comparison of survival between the study participants (n=95) and natural history populations (n=49). Natural history data were obtained from a contemporaneous population with congenital athymia who were observed from 1991 to 2017 and received only supportive care. The Kaplan-Meier estimated survival rates for the study participants who received allogeneic processed thymus tissue was 77% (95% CI 0.670 to 0.841) at 1 year and 76% (95% CI 0.658 to 0.832) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. In comparison, the 2-year survival rate was 6%, with all patients dying by 3 years of age in the external historical control. In addition to the observed survival benefit, the efficacy is also supported by evidence of immune reconstitution based on decreased frequency and severity of infections. Overall, there were 29 deaths following treatment in the study population. The most common cause of death was infection and most of these deaths occurred during the first year after treatment, which is not unexpected as immune reconstitution following treatment takes about 6 to 12 months after transplantation. No major limitations in the study relevance were identified. Limitations in study design and conduct relates to the lack of RCTs. Congenital athymia is an ultra-rare disorder and therefore conducting randomized trials would be challenging. The evidence 1) included data from a large number of study participants, especially given the rarity of the disease with a long duration of follow-up (over 25 years), 2) the natural history is uniform and well-characterized, and 3) most importantly, there was a large survival effect that was consistent and persistent in this otherwise rapidly fatal disease, despite the heterogeneous underlying genetic anomalies and diverse comorbid conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

OBJECTIVE

The objective of this evidence review is to assess whether treatment with allogeneic processed thymus tissue-agdc improves the net health outcome in pediatric individuals with congenital athymia.

PRIOR APPROVAL

Not applicable.

POLICY

Allogeneic processed thymus tissue-agdc is considered **medically necessary** for pediatric individuals with congenital athymia if they meet criteria 1 through 8:

1. Are 21 years old or younger at the time of surgical procedure.
2. Confirmed diagnosis of congenital athymia via flow cytometry documenting fewer than 50 naïve T cells/mm³ in the peripheral blood or less than 5% of total T cells being naïve in phenotype.
3. Diagnosis of severe combined immunodeficiency has been ruled out.
4. Documentation that following infection control measures can reasonably be maintained until the development of thymic function is established. (See policy guidelines for additional details).
 - a. Antimicrobial prophylaxis to prevent bacterial, fungal, and viral infections
 - b. Immunoglobulin replacement therapy
 - c. Strict infection control, sanitation, and isolation protocols to limit exposure to infectious pathogens
5. Absence of comorbidities, in the opinion of the treating clinician, that are reasonably likely to result in severe complications, including death from administration of allogeneic processed thymus tissue (for example, pre-existing renal impairment, or cytomegalovirus or Epstein-Barr virus infection).
6. Screened for anti-human leukocyte antigen (HLA) antibodies prior to receiving allogeneic processed thymus tissue-agdc. Individuals testing positive for anti-HLA antibodies should receive allogeneic processed thymus tissue-agdc from a donor who does not express those HLA alleles.
7. If the individual has received a prior hematopoietic cell transplantation or a solid organ transplant, HLA matching of allogeneic processed thymus tissue-agdc to recipient alleles that were not expressed in the donor is required.
8. Has not previously received thymus tissue implantation for the treatment of congenital athymia in their lifetime.

Allogeneic processed thymus-agdc is considered **investigational** when the above criteria are not met.

Allogeneic processed thymus-agdc is considered **investigational** for all other indications.

Repeat treatment with allogeneic processed thymus-agdc is considered **investigational**.

POLICY GUIDELINES

Recommended Dose

The recommended dose range is 5,000 to 22,000 mm² of allogeneic processed thymus tissue-agdc/m² recipient body surface area.

Dosing Limits

1 surgical implantation per lifetime.

Other Considerations

Allogeneic processed thymus tissue-agdc is administered by a single surgical procedure. The dosage is determined by the total surface area of the allogeneic process thymus tissue-agdc slices and recipient body surface area. A slice is defined as the contents on a single fiber membrane; the allogeneic processed thymus tissue-agdc slices are variable in size and shape. The manufacturer calculates the dose in advance of the specific individual; the amount of product provided is adjusted at the manufacturing facility to ensure the maximum dose for the individual cannot be exceeded. Up to 42 cultured allogeneic processed thymus tissue-agdc slices will be provided to each individual. Individuals with evidence of maternal engraftment or an elevated response to phytohemagglutinin should be receive allogeneic processed thymus tissue-agdc with immunosuppressive medications.

To decrease the risk of graft-versus-host disease, immunosuppressive therapy should be administered prior to and/or after treatment according to the disease phenotype and pre-treatment phytohemagglutinin response in accordance with the recommendations in Table 2 and 3 of the product label.

Immune reconstitution sufficient to protect against infection is unlikely to develop prior to 6 to 12 months after treatment with allogeneic processed thymus tissue-agdc. For some individuals, it may take up to 2 years.

Immunizations should not be administered in individuals who have receive allogeneic processed thymus tissue-agdc until the individual's immune-function has been restored. It is recommended prescribers reference the following criteria before deciding to administer an inactivated vaccine: immunosuppressive therapies have been discontinued, immunoglobulin replacement therapy has been discontinued, the total CD4+ T cell count is > 200 cells/mm³, and there are more CD4+ T cells than CD8+ T cells. It is recommended that no more than 2 inactivated vaccines be given per month. Live vaccines should not be administered until individuals have met the recommended criteria for inactivated vaccines and received vaccinations with inactivated agents.

Coding

See the [Codes](#) table for details.

BACKGROUND

Congenital Athymia

Congenital athymia (CA) is an ultra-rare condition in which the individuals are born without a functioning thymus. Estimated incidence in the United States is approximately 17 to 24 infants for every 4 million. The thymus is crucial for the development, selection and maturation of T cells, which are essential in effectively fighting infection and regulating the immune system. Without a functioning thymus, individuals are profoundly immunodeficient, at significant increased susceptibility for infection, and greater tendency to develop autologous graft-versus-host disease (GVHD). These infections and autoimmune conditions can be fatal, and with only supportive care, children with congenital athymia typically do not survive beyond 2 to 3 years of age. Congenital athymia may be associated with other conditions such as: DiGeorge syndrome (with or without 22q11.2 deletion syndrome); mutations in the genes TBX1, CHD7, (CHARGE syndrome), and FOXP1 (FOXP1 deficiency); and diabetic embryopathy.

Diagnosis

Currently, all 50 states in the USA offer newborn screening testing that identifies T cell receptor excision circles. This test may identify infants who have congenital athymia in addition to severe combined

immunodeficiency (SCID). Confirmatory diagnosis requires confirmation of low naïve T cells by flow cytometry.

Diagnosis of congenital athymia requires confirmation of profoundly low naïve T cells by flow cytometry and genetic evaluation after initial positive results via severe combined immunodeficiency (SCID) newborn screening. Individuals with congenital athymia will have less than 50 naïve T cells per cubic millimeter (mm³) or naïve T cells comprising less than 5% of the total T cells. However, congenital athymia individuals and a subset of SCID individuals also present with a lack of T cells but normal levels of B cells and Natural Killer cells (T-B⁺ NK⁺). To differentiate these individuals, a genetic panel for known T-B⁺ NK⁺ SCID gene mutations, genetic testing to identify gene associated with either condition or testing of hematopoietic stem cells using an artificial thymic organoid (ATO) system can be used. Accurate identification of the causes for immunodeficiency in these individuals is important as to ensure appropriate treatment decisions (e.g., receipt of hematopoietic stem cell transplant vs. cultured thymus tissue implantation).

Treatment

Medical treatment of congenital athymia typically focuses on supportive care. Strict infectious disease prevention measures (e.g., masks, sterile gowns, gloves, frequent handwashing), isolation, and antimicrobial prophylaxis to prevent bacterial, viral and fungal infections are critical. Because B cell function is usually reduced, immunoglobulin replacement should be considered. Immunosuppressive agents including steroids or calcineurin inhibitors may be required to manage inflammatory reactions and reduce the risk of autologous GVHD. Hematopoietic stem cell transplantation has been performed in congenital athymia, but the efficacy is low.

Regulatory Status

On October 8, 2021, allogeneic processed thymus tissue-agdc (Rethymic®; Enzyvant now Sumitomo Pharma) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of congenital athymia in pediatric patients.

RATIONALE

This evidence review was created in December 2022 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 2025.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances,

nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Congenital Athymia

Clinical Context and Therapy Purpose

The purpose of allogeneic processed thymus-agdc in pediatric individuals with congenital athymia is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- Treatment offers a novel mechanism of action or approach that may allow successful treatment of many individuals for whom other available treatments are not available.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is pediatric individuals who are diagnosed with congenital athymia.

Interventions

The therapy being considered is allogeneic processed thymus tissue-agdc. The tissue culture is obtained from an unrelated infant donor ≤9 months old undergoing cardiac surgery where thymus tissue removal is necessary. The tissue is aseptically processed and cultured to reduce donor thymocyte levels and maintain similar overall tissue organization, viability, and retention of cell types necessary for product function. Following 12 to 21 days of culture, the tissue slices are collected for transplantation. These slices are then surgically implanted into individuals with congenital athymia. The treatment is intended to reconstitute immunity in individuals who are athymic. The proposed mechanism of action involves the migration of recipient T cell progenitors from the bone marrow to the implanted tissue slices, where they develop into naïve immunocompetent recipient T cells. Evidence of thymic function can be observed with the development of naïve T cells in the peripheral blood; this is unlikely to be observed prior to 6 to 12 months after treatment with allogeneic processed thymus tissue-agdc.

Comparators

Prior to the availability of allogeneic processed thymus tissue-agdc, there was no U.S. Food and Drug Administration (FDA) approved treatment for congenital athymia. Medical management focused on supportive care such as infectious disease prevention measures, antimicrobial prophylaxis, isolation, immunoglobulin replacement and immunosuppressive management.

Outcomes

The general outcomes of interest are disease-specific survival, change in disease status, quality of life (QOL), treatment-related mortality and treatment related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Studies

Primary evidence of safety and effectiveness was based on accumulated data from multiple clinical trials conducted over a period of 28 years at a single center, Duke University. The evidence included integrated data from 10 prospective, single-center, open-label studies that evaluating a total of 105 patients. Ninety-five patients were included in the primary efficacy analysis. Trial characteristics and results are summarized in Tables 1 and 2, respectively. Patient demographics and baseline characteristics were similar between studies. Median age was 8.5 months (range: 33 days to 2.9 years); 59% were male; 70% White, 22% Black, 4% Asian/Pacific Islander, 2% American Indian/Alaskan Native and 2% multi-race. Immunosuppressive therapy was administered to patients based on disease phenotype and pre-allogeneic processed thymus tissue-agdc phytohemagglutinin (PHA) response. No re-treatment occurred.

The primary evidence of efficacy is based on a comparison of 1-year survival between the study participants and natural history populations. Natural history data were obtained from a contemporaneous population of 49 patients with congenital athymia who were observed from 1991-2017 and received only supportive care. The natural history population was sufficiently similar to the study populations who received the intervention. The Kaplan-Meier estimated survival rates for the study participants who received allogeneic processed thymus tissue was 77% (95% CI 0.670 to 0.841) at 1 year and 76% (95% CI 0.658 to 0.832) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. In comparison, the 2-year survival rate was 6%, with all patients dying by 3 years of age in the external historical control. In addition to the observed survival benefit, the efficacy is also supported by evidence of immune reconstitution based on decreased frequency and severity of infections, evidence of thymopoiesis on biopsy, increasing numbers of naïve CD3, CD4 and CD8 T-cells, emergence of diverse T-cell receptor variable beta repertoires and increased T cell proliferation in response to antigen/mitogen. Only outcomes related to infection are summarized in Table 2. Based on the Wilcoxon signed-rank test, there was a significant difference in the frequency of infection with an onset within 6 months versus an onset within 6 to 12 months post-transplantation ($p < .001$). Reduction in the frequency of infections and serious infections in year 2 compared to year 1 was also significant. Infections are clinically meaningful, proximal manifestations of congenital athymia. Therefore, a decrease in frequency of infections and severe infections provides data to support that clinically meaningful immune reconstitution has occurred.

Overall, there were 29 deaths following treatment in the study population. The most common cause of death was infection ($n=14$, 48%), and most of these deaths occurred during the first year after treatment, which is not unexpected as immune reconstitution following treatment takes about 6 to 12 months after transplantation. There were 3 deaths possibly related to study treatment; 2 were attributed to

immunosuppressive agents, and one was due to cytomegalovirus (CMV) that may have been acquired from the donor thymus tissue.

Table 1. Key Characteristics of Pivotal Trial

Study	Study Type	Country	Sites	Dates	Participants	Treatment	Follow-Up
Markert et al. (2022)	Prospective, single-center, open-label studies	U.S.	1 site	1993-2020	N = 105 (N = 95 in the primary efficacy analysis)^a Inclusion Criteria • Congenital athymia^b • Confirmed athymia^c Exclusion Criteria • Heart surgery within 4 weeks before administration of CTT or anticipated within 3 months after administration of CTT • Poor surgical candidacy as determined by the surgeon or anesthesiologist • HIV infection • Prior attempts at immune reconstitution • Ventilator dependence • CMV infection for patients requiring immunosuppression	Allogeneic processed thymus tissue-agdc in a single surgical procedure at a dose of 4,900 to 24,000 mm ² /recipient BSA in m ² .	Median follow-up of 10.7 years

BSA: body surface area; cDGA: complete DiGeorge anomaly; CMV: cytomegalovirus; CTT: cultured thymus tissue; HIV: human immunodeficiency virus; SCID: severe combined immunodeficiency.

a Ten patients were excluded from the primary efficacy analysis: 2 because they were ultimately diagnosed with SCID, 6 because they received a previous hematopoietic stem cell transplantation or fetal transplant and 2 because their diagnosis was not definitive.

b Defined as cDGA in which patients had athymia plus either a congenital heart defect or hypocalcemia/hypoparathyroidism or FOXP1 deficiency. cDGA included 22q11.2ds, CHARGE syndrome, other genetic defects associated with congenital athymia, and diabetic embryopathy.

c Athymia defined as circulating CD3+CD45RA+CD62L+ T-cell count lower than 50/mm³ or less than 5% of the total T-cell count on 2 separate flow cytometry analyses (1 performed within 3 months and 1 performed within 1 month before administration of cultured thymus tissue), unless they were enrolled in the expanded access protocol, according to which the naive T-cell could be higher than 50 mm³

Table 2. Summary of Results from Pivotal Studies

Study	Kaplan-Meier estimated survival rate	Infection/Serious Infection			
		< 6 months (n=95)	6-12 months (n=80)	Year 1 (n=95)	Year 2 (n=73)
Allogeneic processed thymus tissue (n=45)	Year 1: 77% (0.670 to 0.841) Year 2: 76% (0.658 to 0.832)	Number of infections: 346 Number of participants (%): 83 (87.4%) Number of serious infections: 135 Number of participants with serious infections: 55 (57.9%)	Number of infections: 109 Number of participants (%): 45 (56.3%) Number of serious infections: 51 Number of participants with serious infections: 25 (31.3%)	Number of infections: 455 Number of participants (%): 89 (93.7%) Number of serious infections: 186 Number of participants with serious infections: 63 (66.3%)	Number of infections: 99 Number of participants (%): 34 (46.6%) Number of serious infections: 58 Number of participants with serious infections: 23 (31.2%)
External control (n=45)	Year 2: 6% Year 3: 0	Data not collected/reported	Data not collected/reported	Data not collected/reported	Data not collected/reported

The purpose of the study limitations tables (Table 3) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. No major limitations in the study relevance were identified. Limitations in study design and conduct relates to the lack of RCTs. However, congenital aytmia is an ultra-rare disorder and therefore conducting randomized trials would be challenging. However, the evidence 1) included data from a large number of study participants, especially given the rarity of the disease with a long duration of follow-up (over 25 years), 2) the natural history is uniform and well- characterized, and 3) most importantly, there was a large survival effect that was consistent and persistent in this otherwise rapidly fatal disease, despite the heterogenous underlying genetic anomalies and diverse comorbid conditions.

Table 3. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Markert et al. (2022)	1. Participants not randomly allocated 2. Allocation not concealed; 3. Allocation concealment unclear;	1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by				

	4. Inadequate control for selection bias.	treating physician.				
--	---	---------------------	--	--	--	--

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4.

Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Congenital Athymia

Primary evidence of safety and effectiveness was based on an integrated analysis from 10 multiple prospective, single-center, open-label studies conducted over a period of 28 years at a single center that included 95 patients with a diagnosis of congenital athymia. The primary evidence for efficacy was based on a comparison of survival between the study participants and natural history populations. Natural history data were obtained from a contemporaneous population of 49 patients with congenital athymia who were observed from 1991-2017 and received only supportive care. The Kaplan-Meier estimated survival rates for the study participants who received allogeneic processed thymus tissue was 77% (95% CI, 0.670 to 0.841) at 1 year and 76% (95% CI, 0.658 to 0.832) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. In comparison, the 2-year survival rate was 6%, with all patients dying by 3 years of age in the external historical control. In addition to the observed survival benefit, the efficacy is also supported by evidence of immune reconstitution based on decreased frequency and severity of infections. Overall, there were 29 deaths following treatment in the study population. The most common cause of death was infection and most of these deaths occurred during the first year after treatment, which is not unexpected as immune reconstitution following treatment takes about 6 to 12 months after transplantation. No major limitations in the study relevance were identified. Limitations in study design and conduct relates to the lack of RCTs. Congenital athymia is an ultra-rare disorder and therefore conducting randomized trials would be challenging. The evidence 1) included data from a large number of study participants, especially given the rarity of the disease with a long duration of follow-up (over 25 years), 2) the natural history is uniform and well- characterized, and 3) most importantly, there was a large survival effect that was consistent and persistent in this otherwise rapidly fatal disease, despite the heterogenous underlying genetic anomalies and diverse comorbid conditions.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or

National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

REFERENCES

1. Rethymic. About Congenital Athymia. 2024; <https://www.rethymic.com/hcp/what-is-congenital-athymia/>. Accessed December 4, 2025.
2. Gordon J, Manley NR. Mechanisms of thymus organogenesis and morphogenesis. *Development*. Sep 2011; 138(18): 3865-78. PMID 21862553
3. Markert ML, Hummell DS, Rosenblatt HM, et al. Complete DiGeorge syndrome: persistence of profound immunodeficiency. *J Pediatr*. Jan 1998; 132(1): 15-21. PMID 9469994
4. Markert ML, Marques JG, Neven B, et al. First use of thymus transplantation therapy for FOXP1 deficiency (nude/SCID): a report of 2 cases. *Blood*. Jan 13 2011; 117(2): 688-96. PMID 20978268
5. Markert ML, Devlin BH, Alexieff MJ, et al. Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. *Blood*. May 15 2007; 109(10): 4539-47. PMID 17284531
6. Collins C, Sharpe E, Silber A, et al. Congenital Athymia: Genetic Etiologies, Clinical Manifestations, Diagnosis, and Treatment. *J Clin Immunol*. Jul 2021; 41(5): 881-895. PMID 33987750
7. Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. *J Allergy Clin Immunol*. Feb 2022; 149(2): 747-757. PMID 34362576
8. Rethymic prescribing information. Enzyvant Therapeutics, Inc Revised 10/2021. <https://www.fda.gov/media/152912/download?attachment> Accessed December 4, 2025.
9. Summary Basis for Regulatory Action for Rethymic. Available at <https://www.fda.gov/media/153729/download>
10. Bonilla F, Khan D, Ballas Z, et. a. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol* Volume 136, Number 5 2015
11. Hayes Inc. Evolving Evidence Review Rethymic (Enzyvant Therapeutics Inc.) for Congenital Athymia. June 2023
12. UpToDate. DiGeorge (22q11.2 deletion) syndrome: Management and prognosis. Christine M. Seroogy M.D., Topic last updated June 11, 2025. Also available at <https://www.uptodate.com> Accessed December 4, 2025.
13. U.S. Food and Drug Administration. Summary Basis for Regulatory Action for Rethymic. 2021; <https://www.fda.gov/media/153729/download>. Accessed December 4, 2025.

CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT	None	
HCPCS		
	C9399	Unclassified drugs or biologicals (may be utilized for Rethymic® implant)
	J3490	Unclassified drugs (may be utilized for Rethymic® implant)
	J3590	Unclassified biologics (may be utilized for Rethymic® implant)
Type of Service	Medical	
Place of Service	Inpatient	

POLICY HISTORY

Date	Action	Action
December 2025	Annual Review	Policy Renewed
December 2024	Annual Review	Policy Revised
December 2023	Annual Review	Policy Revised
December 2022		New Medical Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.